# REMARKS

## I. Status of Claims:

Claims 1-10, 17-24, and 29-46 remain pending in the case. Claims 1-10, 22-24 and 32-34 are under examination in this application, claims 11-16 and 25-28 having been previously canceled and claims 17-21, 29-31 and 35-46 withdrawn from consideration. Claims 3, 4, 21, and 23 are amended herein. Support for these amendments can be found throughout the application as filed, e.g., in Figure 1. No new matter is added.

## II. Rejections Under 35 U.S.C. § 103(a):

Claims 1-10, 22-24 and 32-34 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Ozaki et al., *Blood*, 102:933a (2003) ("Ozaki") in view of Kortt et al., *Biomol. Eng.*, 18:95-108 (2001) ("Kortt"). Applicants respectfully traverse.

In dismissing Applicants' arguments filed in the Response dated June 30, 2009, the Office Action at page 5 states in relevant part:

> In response to this argument, the examiner agrees that Kortt teaches a number of antibody molecules however, the relevant molecules to this discussion are at the bottom of page 95 and the top of page 96 where Kortt states:
>
> *"Recent design variations of engineered antibodies have included reduction in size to single-chain Fvs, dissection into minimal binding fragments such as VH domains and rebuilding of scFvs into multivalent high-avidity oligomeric scFvs (Figure 1)."*
>
> In looking at Figure 1 the portion labeled "Bivalent scFv fragments" is clearly an sc(Fv)2 because the linkers L1 and L3 join the portions of the scFv and the linker L2 joins the two scFv molecules in to a single chain. The discussion of the length of the linker in figure 3 is relevant to the sc(Fv)2 molecule because Kortt makes clear that the length of the linker is the portion of the molecule responsible for the structural folding and formation of the different antibody structures and Kortt provides several linkers in Figure 3 for the production of these antibodies. Further, Kortt discusses the multivalent molecules in figure 1 provide a significant increase in functional affinity (page 96 column 2). Thus, the Kortt reference does not teach away from the instant claims as asserted by

applicant, but rather provides information towards producing a number of different antibody structures.

We address each of these contentions below.

First, the sentence quoted in the Office Action from Kortt is merely an introductory comment regarding design variations of engineered antibodies that are illustrated in Figure 1. To be clear, Applicants are not suggesting that sc(Fv)2 molecules were not known in the art at the time of the filing of the instant application. Rather, Applicants contend that Kortt provides no reason to produce an sc(Fv)2 version of the 2D7 diabody (2D7-DB) of Ozaki. In fact, as described in greater detail below, Kortt actually teaches away from doing so. Furthermore, other than this general comment about the existence of different types of intact immunoglobulins, immunoglobulin fragments, and antibody conjugates, and the illustration of various structures in Figure 1, Kortt is entirely devoted to describing the creation of non-covalent oligomeric forms of Fv modules (diabodies, triabodies, and tetrabodies) and explaining that they are significantly advantageous over the other types of antibody molecules shown in Figure 1.

Second, Applicants note that the Office Action appears to consider the discussion of the length of linkers in Figure 3 to be relevant to sc(Fv)2 molecules "because Kortt makes clear that the length of the linker is the portion of the molecule responsible for the structural folding and formation of the different antibody structures and Kortt provides several linkers in Figure 3 for the production of these antibodies." Applicants point out that Figure 3 illustrates linkers used to join the VH domain and VL domain of a scFv monomer. This is apparent from the diagram at the top of Figure 3, which shows a polypeptide structure containing just two V domains (one VH and one VL) joined by the linker. The pel B leader at the N-terminus and a FLAG tag at the C-terminus are an indication that the entire structure is represented, and thus no other V domains are included. The references to "scFv-multimers" in the legend to Figure 3 denotes the sorts of multimers into which such scFv monomers can self-assemble, i.e., non-covalent multimers such as diabodies, triabodies and tetrabodies. This is clear from the detailed discussion on pages 97-99 of Kortt regarding how linker length influences whether an scFv tends to fold on itself and remain monomeric, or instead associate with 1, 2, or 3 copies of itself to form one of these

noncovalent multimers. Nothing in Figure 3 or the discussion thereof relates to the effects of linker length on sc(Fv)2 structure or function. While it may be true that linker length is important to the function of sc(Fv)2 molecules, that is not discussed in Figure 3 nor anywhere else in Kortt. Thus, the Examiner's reliance on Figure 3 of Kortt as evidence that Kortt discussed the importance of linker length in sc(Fv)2 is misplaced.

Third, the Office Action states that "Kortt discusses the multivalent molecules in figure 1 provide a significant increase in functional affinity (page 96 column 2.)." The term "functional affinity" or avidity as used on page 96, column 2, refers to the molecule's binding ability attributable to the number of antigen binding domains, i.e., the valency of the antibody. (See Kortt's statement that the increase in functional affinity is provided "via multivalent binding.") Applicants note that Ozaki teaches a 2D7 IgG monoclonal antibody and a 2D7 diabody. Both an IgG and a diabody possess two antigen binding domains (each antigen binding domain being composed of one VH and one VL). So does an sc(Fv)2. Thus, one of ordinary skill in the art would not expect an sc(Fv)2 to have increased functional affinity compared to an IgG or a diabody. If increasing functional affinity of an IgG or diabody were the goal, one might seek to modify it into a triabody or tetrabody or IgM (all of which have more than two antigen binding domains), but not an sc(Fv)2. The motivation to produce an sc(Fv)2 that the Examiner sees in Kortt simply does not exist.

Applicants again emphasize that, by teaching the disadvantages of sc(Fv)2 compared to diabodies, Kortt actually *teaches away* from the presently claimed compositions. Significantly, Kortt states at page 104, left column:

> Although several groups continue to develop covalent scFv dimers [*i.e., sc(Fv)2*], we predict that diabodies will be more stable than these scFv dimers. Indeed, the linkers in diabodies and triabodies are apparently relatively inaccessible to proteases compared with the long linkers required to join two monomeric scFv (Figs. 1 and 5).

Kortt clearly states his view that sc(Fv)2 have the disadvantage of being more susceptible to proteases than diabodies and triabodies, and thus less stable than the latter. Furthermore, Kortt teaches at page 106, left column:

> Pre-clinical biodistribution studies have shown that **diabodies offer significant advantages over (scFv)2** and F(ab)2 for imaging and therapy and will no doubt be in clinical trials within 12-24 months. (Emphasis supplied)

Applicants submit that nothing in Ozaki nor in Kortt could be read as a motivation to produce an sc(Fv)2 version of Ozaki's 2D7 diabody. Quite to the contrary: Kortt presents reasons one would prefer the diabody, and not even bother to consider making a sc(Fv)2.

In distinct contrast to the unambiguous expectation in Kortt that an sc(Fv)2 would be less stable than a diabody and that *in vivo* pharmacokinetics depend on the size of antibodies, Applicants have surprisingly found that the 2D7sc(Fv)2 disclosed in the present application has a longer half-life *in vivo* compared with the corresponding 2D7 diabody of Ozaki. See Example 7 at page 24 of the substitute specification filed June 9, 2006. Following intravenous injection into mice, 2D7sc(Fv)2 exhibited a half life of 2.30 hours, compared to 1.64 hours for the 2D7 diabody (page 24, lines 27-30). Thus, despite the teachings of Kortt regarding instability and pharmacokinetics, Applicants' findings show unexpected advantages of sc(Fv)2 having a binding activity against HLA.

As the Examiner is no doubt aware, the U.S. courts recognized long ago that a teaching-away in the art is particularly powerful evidence that the art does not supply the necessary motivation to make the claimed invention. See, e.g., *United States v. Adams*, 383 U.S. 39, 51-52 (1966). The holding in *Adams* regarding teaching-away is still very much the law; indeed, it was cited with approval in the recent Supreme Court case, *KSR v. Teleflex*, 127 S.Ct. 1727, 1740 (2007). The same two cases (and many others) also stated that results that are unexpectedly better than what the art would have predicted constitute further cogent evidence of non-obviousness. Where, as here, the Examiner has not begun to make a case that the art provided a motivation to fashion a sc(Fv)2 form of the 2D7 diabody (there being no reason to expect an improvement in either binding or stability upon doing so), and where the cited art actually pointed out expected <u>disadvantages</u> of sc(Fv)2 compared to diabodies, it is clear that a *prima facie* case of obviousness has not been established. The fact that Applicants demonstrated results

that were plainly far better than the cited art would have led one to expect is further evidence that the rejection is unwarranted.

The above evidence and arguments apply to all of the rejected claims, and mandate withdrawal of the obviousness rejection with respect to all claims. Applicants note that there are many other reasons supporting withdrawal of the rejection as to particular claims. For example, claims 22-24 and 32-34 are drawn to pharmaceutical compositions. Rather than address why the art renders the claimed pharmaceutical compositions obvious, the Office Action merely alleges that the recitation of "pharmaceutical composition" in these claims "is an intended use of the claimed antibody and as such receives no patentable weight." Applicants point out that the term "pharmaceutical composition" operates as a limitation that excludes compositions that would not be appropriate for pharmaceutical use. For example, the pharmaceutical composition of claim 22 plainly would not encompass a composition containing significant levels of potentially harmful contaminants (such as endotoxin) remaining from a cell culture in which the antibody of claim 1 was produced, contaminants that may well be present unless carefully removed. It is not clear to Applicants why the Examiner believes otherwise. If the rejection of these claims is to be maintained despite the arguments presented above that apply to all of the claims, Applicants ask the Examiner to address this point.

Turning next to the new rejection of claims 8-10, the Office Action states that Ozaki teaches a 2D7 antibody clone that binds to HLA and has a cell death inducing function, a cell growth inhibitory function, and an anti-myeloma function. The Office Action also states that Applicants' specification at page 2, lines 26-36, discloses that the 2D7 antibody clone was used to produce sc(Fv)2 as presently claimed. *See*, Office Action at page 6.

*Claim 8* is drawn to an sc(Fv)2 comprising heavy chain variable regions that comprise complementarity determining region (CDR) 1, 2, and 3 that consist of the amino acid sequences of SEQ ID NOs: 3, 4, and 5. *Claim 9* covers an sc(Fv)2 comprising light chain variable regions that comprise CDR 1, 2, and 3 that consist of the amino acid sequences of SEQ ID NOs: 6, 7, and 8. *Claim 10* is drawn to an sc(Fv)2 comprising heavy chain variable regions that comprise CDR1, 2, and 3 consisting of the amino acid sequences of SEQ ID NOs: 3, 4, and 5, and light

chain variable regions that comprise CDR 1, 2, and 3 consisting of the amino acid sequences of SEQ ID NOs: 6, 7, and 8.

The focus when making a determination of obviousness is on what the person of ordinary skill in the art would have known from the teachings of the cited reference(s) and what she would have been able to do with that knowledge. The CDRs recited in claims 8-10 were derived from an antibody named "2D7." Ozaki describe experiments using a 2D7 antibody and a 2D7 diabody. However, Ozaki does not provide **any** sequence of the 2D7 antibody, the 2D7 diabody, or the CDRs of 2D7. Furthermore, Ozaki does not disclose that a clone expressing the 2D7 antibody or diabody was deposited with a depository or otherwise made available to the public. Without access to the antibody or diabody, or to cells expressing the antibody or diabody, or to the sequence of the antibody, diabody, or CDRs, it would have been essentially impossible for one of ordinary skill in the art to make an antibody having the precise sets of CDRs specified in the present claims. Thus, although Ozaki discloses the existence of the antibody named "2D7" and the diabody named "2D7DB", that information is insufficient to make it obvious to one of ordinary skill to produce the sc(Fv)2's encompassed by claims 8-10. Applicants' disclosure cannot be used to provide the required information missing from Ozaki in order to render Applicants' claims obvious.

For at least the foregoing reasons, Applicants respectfully request that the outstanding rejections under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

## CONCLUSION

Applicants respectfully submit that all pending claims are in condition for allowance, and therefore request the timely issuance of a Notice of Allowability.

Applicants petition for a one-month extension of time to respond to the outstanding Office Action. No additional fees are believed to be due. Please apply any required charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-0166US1.

If the Examiner has any questions regarding this application, she is invited to call the undersigned at the telephone number given below.

Respectfully submitted,

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